# REMARKS

## I. THE STATUS OF THE CLAIMS

Claims 1-6, 8-19 and 21-25 are pending in the application. Claims 1-6, 8-17, 19 and 21-25 are rejected. Claim 18 is withdrawn from consideration.

## II. THE REJECTION UNDER 35 U.S.C. § 103

The final Office Action rejects claims 1-6, 8-17, 19 and 21-25 under 35 U.S.C. § 103 as being obvious over Gowan. (U.S. Patent No. 5,374,659), Gergely et al. (U.S. Patent No. 5,834,019), Patel et al. (U.S. Patent No. 6,569,463), Eichman (U.S. Patent No. 5,980,882) and Hagemann et al. (U.S. Patent No. 5,211,957). Applicants respectfully traverse the rejection.

The cited references, alone or combined, do not disclose or suggest the claimed invention. The claimed invention is A pharmaceutical aqueous suspension comprising:

a) a therapeutically effective amount of suspended solid particles in crystal form comprising at least one active ingredient;

b) a thickener;

c) a uniformly dispersed nucleation inhibitor, wherein said nucleation inhibitor reduces growth rate of said active ingredient compared to suspensions not containing a nucleation inhibitor and wherein said nucleation inhibitor is polyvinylpyrrolidone; and

d) at least one amino polycarboxylic acid compound;

wherein the pharmaceutical aqueous suspension has a pH of about 3.7 to about 8; and

wherein the amino polycarboxylic acid compound imparts improved pH and viscosity stability to the pharmaceutical aqueous suspension.

Gowan discloses an aqueous pharmaceutical suspension that consists essentially of from about 0.2 % to about 20 % of a water insoluble pharmaceutical active, xanthan gum; pregelatinized starch; polyoxyethylene sorbitan monooleate; a taste masking composition selected from sugar, sweet polyhydric alcohol, glycerin, artificial sweetner, flavoring agent and mixtures thereof; and water. See col. 2, lines 15-25. Gowan discloses that the pH is preferably between 3 and 5 to prevent microbial growth and to add stability to the product. See col. 5, lines 3-12. As recognized in the final Office Action, Gowan does not disclose the use of polyvinylpyrrolidone as a nucleation inhibitor and the use of an amino polycarboxylic acid compound to impart improved pH and viscosity stability in a pharmaceutical composition.

With regard to the nucleation inhibitor, the specification discloses that "It has additionally been found that the suspension can be further stabilized by the addition of a nucleation inhibitor that is believed to prevent the growth of particles." See corresponding published application no. 20050069590 at paragraph [0046]. The specification also discloses:

> The nucleation inhibitor compound or compounds affects the rates of nucleation and growth, depending upon the nature of the surfaces and the structures of the adsorbed molecules. The degree of inhibition varies with the driving force for crystallization, and the mechanisms of the reactions may also be different in the presence of additives. Polyvinylpyrrolidone, also known as PVP, Polyvidone and Povidone has been found to be a particularly advantageous nucleation inhibitor.
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> PVP is believed, without intending to be bound by theory, to reduce the rate of sedimentation by preventing the growth of pharmaceutical particles. Ostwalt ripening provides for the growth of large particles at the expense of small ones. This effect is due to a difference in the solubility rate of the different size particles. Since the solution rate of the smaller nucleated particles is greater than that of the large crystals, dissolution of smaller particles creates a metastable state of saturation and causes eventual growth from solution onto the edge of large particles until more thermodynamically stable distribution of particle sizes is achieved. In the case of the formulations described herein, it has been found that PVP reduces the growth rates and rate of increase in particle size. The effects are especially significant for formulations that must be subjected to repeated freeze/thaw temperature cycling.

See corresponding published application no. 20050069590 at paragraphs [0053]-[0054].

With regard to the amino polycarboxylic acid compound, the specification discloses:

> Stabilizing the suspension of water insoluble pharmaceutical active ingredients is a key component of the present invention. It has been found by the present inventors, that *the storage stability of the suspension can be surprisingly enhanced by the addition of at least one selected amino polycarboxylic acid compounds*. At least some such compounds, particularly EDTA, are known for use as chelating agents. EDTA has not been previously described as being suitable for improving pH and viscosity stability in liquid suspensions.

See corresponding published application no. 20050069590 at paragraphs [0046] (emphasis added).

With regard to the nucleation inhibitor and the amino polycarboxylic acid compound, the specification discloses:

> The suspension of this example *exhibited superior chemical and physical stability under stress stability conditions compared with suspensions not containing an amino carboxylic acid or a nucleation inhibitor*. Additionally, the suspensions of this example exhibited acceptable taste and color stability after storage at stressed conditions

See corresponding published application no. 20050069590 at paragraphs [0112] (emphasis added).

Gergely et al., which discloses that loratidine is virtually water insoluble, also does not disclose or suggest the use of polyvinylpyrrolidone as a nucleation inhibitor or the use of an amino

polycarboxylic acid compound to impart improved pH and viscosity stability in a pharmaceutical composition.

Patel et al., which generally discloses that the pharmaceutical compositions disclosed therein can *optionally* include one or more additives (see col. 28, lines 57-67 (emphasis added)), including *optionally* solubilizers, including polyvinylpyrrolidone, which appears in a laundry list of choices (see col. 29, lines 15-65); and/or *optionally* enzyme inhibitors, including EDTA, which appears in a laundry list of choices (see col. 30, lines 11-62), also does not disclose or suggest the use of polyvinylpyrrolidone as a nucleation inhibitor and the use of an amino polycarboxylic acid compound to impart improved pH and viscosity stability in a pharmaceutical composition.

Eichman, which discloses that EDTA is known to stabilize drugs in solution by retarding their oxidation (see col. 2, lines 60-61), also does not disclose or suggest the use of polyvinylpyrrolidone as a nucleation inhibitor and the use of an amino polycarboxylic acid compound to impart improved pH and viscosity stability in a pharmaceutical composition.

Hagemann et al., which discloses within a laundry list, the use of polyvinylpyrrolidone as an excipient that may improve viscosity index and inhibit sedimentation of coated active drug diclofenac (see col. 4, lines 42-62), also does not disclose or suggest the use of polyvinylpyrrolidone as a nucleation inhibitor and the use of an amino polycarboxylic acid compound to impart improved pH and viscosity stability in a pharmaceutical composition.

Reconsideration and withdrawal of the rejection of claims 1-6, 8-17, 19 and 21-25 under 35 U.S.C. § 103 over Gowan, Gergely et al., Patel et al., Eichman and Hagemann et al. are respectfully requested.

## III. CONCLUSION

Early consideration and prompt allowance of the claims are respectfully requested. Should the Office require anything further, it is invited to contact Applicants' representative at the telephone number below.

Respectfully submitted,

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